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Review

Antiretroviral therapy: state of the HAART

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1. Introduction

Between 1996 and 1999, the availability of Potent Antiretroviral Therapy had a dramatic impact on the natural history of HIV, with unprecedented changes in disease progression and mortality seen first in the US (Palella et al., 1998), and subsequently in the European population (Pezzotti et al., 1999).

In the western countries, at least, HIV-1 infection has been turned from an inevitably fatal disease into a chronic condition, manageable over the course of decades.

However, despite the impressive progress to date, much work remains to be done. Even with the most potent regimens available today, there exists a significant proportion of patients who fail to have a complete response after their first line treatment (Montaner et al., 1998); this population is at high risk of experiencing a virologic rebound, and will consequently be less and less responsive to subsequent antiretroviral regimens (Sendi et al., 1999), which is in part due to the limited number of therapeutic options currently available.

Incomplete response rate and limited durability of the response (leading to failure) are not the only shortcomings of the current regimens. Other problems include: the complexity of the regimens, toxicity issues (metabolic disturbances ranking first), cross resistance among drugs of the same class and unfavorable pharmacokinetics These problems are particularly evident in patients with high plasma HIV-1 RNA levels, extensive prior antiretroviral treatment, and advanced disease.

2. The goal of antiretroviral therapy

Data from several studies indicate that the nadir of the virologic response and the rapidity with which virus replication is shut down are strongly predictive of the likelihood of achieving a durable virologic response. In the INCAS trial (Raboud et al., 1998) there was a significant difference in the relative risk of virologic rebound among subjects who achieved a plasma viral load below 20 copies/ml and those with a virologic nadir ≥ 400 copies/ml. The available data suggest that little or no virus evolution occurs in the residual virus population when plasma HIV-1 RNA is persistently suppressed to below the limits of quantification of ultrasensitive assays. In particular, no evidence was found for the emergence of drug resistance mutations when viral sequences recovered from lymph nodes or peripheral blood lymphocytes of these subjects were analysed. By

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contrast, such evolution of drug resistance can be observed in patients who experience occasional 'blips' of plasma HIV-1 RNA above the detection limit.

While the general principle of maximally suppressing viral replication is likely to be incorporated in the next revisions of current therapeutic guidelines, the situation may be different when immunologic response is considered. Indeed, recent data on isolated patients suggest that the persistence of viral antigens may lead to the persistence of both anti-HIV specific helper activity and cytotoxic T cell activity (Lisziewicz et al., 1999), which are present in most individuals with early HIV infection, but decline with prolonged viral suppression (Pitcher et al., 1999). Consequently, one might speculate that the intermittent administration of HAART could represent a way to maintain an effective anti HIV immune response. The same goal might be achieved by utilizing by an early and repeated vaccination with HIV antigenic determinants. Both these hypothesis should be tested in controlled clinical trials before being considered for clinical practice. In the meantime, the aim of antiretroviral therapy remains the suppression of viral load to the lowest level possible and for the maximum amount of time.

3. Antiretroviral strategies

To achieve the goal of a complete suppression of HIV in plasma, at least in subjects on their first antiretroviral regimen, several strategies are now available. These include protease inhibitor (PI)-containing and PI-sparing regimens. PI-containing regimens have several advantages, which include potency, evidence for long-term (>3 years) durability, potentially exploitable drug-drug interactions, widely known toxicity profile and evidence of effectiveness in patients with various plasma HIV-1 RNA levels. Due to these characteristics, PI-containing regimens are the first choice for patients initiating their antiretroviral treatment. Nevertheless, important disadvantages may limit their acceptability. These include: (a) complexity of the regimens, which creates a challenge in terms of adherence; (b) cross-resistance between different PIs, which may limit the utility of the future PI regimens should initial therapy fail and (c) the growing concern over long-term toxicities, including fat redistribution, metabolic abnormalities and unknown effects of these latter on long term cardiovascular morbidity and mortality. For these reasons, and because of the availability of new potent reverse transcriptase inhibitors, PI-sparing regimens have been introduced into clinical research, and clinical practice thereafter.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) have gained in popularity for their potential role in PI-sparing regimens. A durable (48-week) suppression of plasma HIV-1 RNA has been demonstrated for a three-drug regimen including efavirenz (EFV), zidovudine (ZDV), and lamivudine (3TC) (Tashima et al., 1999). These results have provided convincing evidence that NNRTI regimens offer a suitable alternative to PI containing combinations for initial antiretroviral therapy in treatment-naive patients. Consequently, in the most recent version of the Guidelines for the use of Antiretroviral Agents in HIV-infected Adults and Adolescents (USDHHS Panel on Clinical Practices for the treatment of HIV infection) the triple combination of two nucleoside analogues plus efavirenz is considered as a first line regimen, equivalent to the so far 'standard' one (two nucleoside analogues and 1 PI). NNRTI-containing regimens, besides the potential advantage of deferring the introduction of PIs, in some instances allow for a lower pill burden than PI-containing regimens, as is the case for nevirapine (NVP) and EFV. On the other hand, they are not without potential disadvantages. Among these, resistance issues represent the main cause of concern: high-level resistance to NVP and delavirdine (DLV), conferred by a single nucleotide change, appear to emerge with relative rapidity; in addition, important cross-reactivity exists among drugs of the same class. The lack of exhaustive information about long term efficacy and safety represents an additional source of concern, together with the potential limitations of a therapeutic approach targetting only a single viral protein (reverse transcriptase).

Recently the possible use of triple NRTI therapy as a PI-and NNRTI-sparing regimen has been proposed. Most data refer to the combination of abacavir (ABC), zidovudine and 3TC, which has resulted in durable (48-week) virologic responses (Fischl et al., 1999). In addition, this combination appears to have equivalent activity to a 'standard' regimen of ZDV/3TC/indinavir (IDV), in terms of virologic activity, when directly compared to it. As with the NNRTIs, the main attraction of an all-NRTI regimen is deferral of the use of PIs, while sparing the NNRTI and placing only a single class of agents 'at risk' for development of resistance. However, also in this case the long-term efficacy and toxicities of multinucleoside regimens are unknown. In addition there is concern over the possible selection of multinucleoside-resistant variants carrying either the Q151M or T69SSS mutation complexes.

With short-term clinical trials indicating comparable potency and efficacy of PI-, NNRTI and all NRTI-containing regimens (Montaner, 1999), the attention should be focussed on the differences with regard to long-term outcome, toxicity, constraints on subsequent regimens, and the effect on viral reservoirs in non-lymphoid compartments. The answers to these questions and the advantages/disadvantages ratio of these different treatment strategies will only come from the results of well-controlled strategic clinical trials, such as ACTG 384, currently conducted by the Adults AIDS Clinical Trials Group (ACTG), and the European INITIO study. Both these large studies are aimed at investigating the effectiveness of not just single regimens, but of different therapeutic pathways, including a first-, second- and eventually third-line regimen.

4. Incomplete virologic response to initial therapy

A major cause for concern is the evidence from several clinical trials that only 70–80% of previously untreated patients achieve complete virologic suppression (defined as plasma HIV-1 RNA below the limits of detection), even with currently available potent regimens. Evidences from several laboratories making use of sensitive molecular assays suggest persistent virus replication in lymphoid tissues in some of these patients. Such persistent replication may be responsible for the occasional 'blips' in plasma HIV-1 RNA that are observed in some patients. Intermittent non-adherence, inter-individual variation in pharmacokinetics, drug-to-drug interactions and inadequate potency of current regimens, all could contribute to persistent virus replication. Given the high rate of HIV-1 replication, the concern is that any residual turnover could lead to rapid repopulation of the HIV-1 quasi species. However, recent anedoctal observations on subjects who had discontinued HMRT for different reasons and showed a vigorous anti-HIV immunological response (Lisziewicz et al., 1999) has elicited some interest in the possibility of an intermittent antiretroviral treatment. The presence of circulating viral antigens might serve as stimulus to the maintenance or re-induction of both specific cytotoxic T lymphocytes and anti-HIV helper activity. As already mentioned, currently these are only speculations which must be tested in controlled clinical trials before being translated into clinical practice.

Looking for reasons that account for incomplete responses, data from several groups suggest that the rate of virus clearance in response to therapy is important. In addition, delays in achieving complete suppression could, in theory, provide an opportunity for the emergence of drug-resistant variants of HIV-1. This situation is particularly worrisome in patients who have very high plasma HIV-1 RNA levels (e.g. $> 100\,000$ copies/ml) at the start of their antiretroviral treatment and in whom the success of current regimens has been relatively disappointing. Several studies are underway to determine whether four-drug regimens that make use of dual-PI combinations or PI-NNRTI combinations (in addition to dual NRTIs) will achieve complete virus suppression in a higher proportion of patients.

5. What is treatment intensification?

One of the strategies which is currently proposed to improve suboptimal responses is the so called 'intensification', which means adding one

or more agents to an existing regimen which has resulted in inadequate suppression of plasma HIV RNA. The aim of this strategy is to achieve a complete response allowing both preservation of drugs that remain potentially useful and sparing future therapeutic options. While this is currently the most common definition of 'intensification', the same approach may be pursued also as salvage for 'early' failure (occurring within the first 20–24 weeks) or as a way to reinforce a complete response. However, this latter approach for the time being is just speculative.

6. Can we simplify therapy?

Given the complexity of many current treatment regimens and the difficulties in treatment adherence experienced by many patients, the question of treatment simplification naturally arises.

Unfortunately, the results so far available have been disappointing, at least for the studies that have been published (Montaner, 1999). Potent antiretroviral treatment with three or four drugs was initiated and continued for 3–6 months. Patients in whom plasma HIV-1 RNA was successfully suppressed to below the limits of detection were then randomized to continue the 'induction' regimen or switch to a 'maintenance' regimen consisting of fewer drugs. In all trials the results were disappointing, patients randomized to maintenance regimens experiencing significantly higher rates of virologic failure as compared to those who remained on their initial therapy.

Several factors could account for the poor outcome of these studies: the duration of induction treatment, the virologic cut off adopted for the switch to a simplified regimen, the low potency of both induction and maintenance regimens. While teaching us that potency must not be sacrificed solely for the sake of improved adherence, the failure of the simplification strategies so far investigated should not discourage from designing further trials, the key issue will be the use of 'simpler' rather than 'weaker' regimens.

7. Treatment failure and salvage regimens

The reasons for treatment failure in HIV-1 infection are multifactorial, including evolution of drug resistance, non-adherence, pharmacokinetic and metabolic factors, inadequate drug potency, and inadequate drug activation (in the case of the NRTIs).

Any discussions on salvage strategies requires a definition of parameters of treatment failure. For the adherent patient on an initial treatment regimen, confirmed detectable plasma HIV-1 RNA (>50 copies/ml) should be considered evidence of treatment failure. Continued treatment with the same regimen in this situation will eventually lead to development of high-level drug resistance, which diminishes the likelihood that salvage regimens will be successful. Thus, for the patient with clear treatment options early switching could maximize the chances for therapeutic success of the next treatment regimen and preserve future options.

The situation differs for patients who are highly treatment-experienced, and for whom fewer options remain. In such cases, a more conservative approach may be warranted. Usually, virologic escape is followed by immunologic deterioration and eventually clinical failure. However, the time lag between HIV RNA rebound and clinical failure varies from patient to patient, and it has become clear that CD4+ cell count may remain high even in the presence of a clear rebound in HIV RNA. Before making any decisions about changes in antiretroviral treatment, it is important to determine why the current regimen is failing, in order to avoid choosing an inappropriate remedy. In particular, factors as drug resistance, inadequate drug exposure due to poor adherence, absorption and pharmacokinetics, persistence of HIV in viral reservoirs, all represent major causes of failure, that should be thoroughly investigated before switching to a different regimen. Once this determination is made, a new drug combination will be chosen according to the suggestions reported in the published guidelines, and based on the general principle that the new regimen should consist entirely of drugs that have not been taken previously. Unfortunately, due to the large degree

of cross-resistance occurring within all antiretroviral drug classes, limited options actually exist, especially for patients experiencing their second or third failure. In this heavily pretreated population, both observational and prospective studies have shown quite disappointing results of any investigated salvage regimens.

Some new approaches are therefore under study. One that is gaining much popularity consists in trying in increasing drug exposure by exploiting the metabolic interaction among protease inhibitors. One example of this approach is the combination of small amounts (100–200 mg twice daily) of ritonavir and indinavir, 800 mg twice daily. This combination leads to a large increase in blood trough levels of indinavir, and also indinavir absorption is not affected by the concomitant ingestion of food (Burger et al., 1999). Preliminary data seem to support the validity of this approach even in antiretroviral-experienced patients with high viral load.

8. The role of resistance testing

In the near future, extensive use of genotypic resistance testing is expected. Though representing a major advantage for the management of HIV patients, the routine use of these tests in the clinical setting has still to be validated. In general, whereas resistance is generally a good predictor of likely drug failure, susceptibility is no guarantee of success. It is becoming a common belief, therefore, that these assays have their major application in predicting which drugs not to use, rather than which are likely to be successful (Perrin and Telenti, 1998). The best current application of resistance testing is therefore for the design of salvage regimens. Indeed, several retrospective and two prospective studies, the VIRADAPT and the GART, have shown that a higher response rate is likely to occur when a salvage regimen is selected on the basis of genotype testing results (Baxter et al., 1999).

A further advantage of resistance testing availability is that the results can also help sparing drugs, when a new regimen has to be designed: while the general principle of changing all drugs in the new combination is still valid, in some cases drug failure may not imply resistance to all agents in that combination (Haviir et al., 1999); in these settings changing one drug only may restore sensitivity to the whole regimen.

However, there are several inherent limitations that should be considered when interpreting the results of both phenotypic and genotypic resistance testing, such as the ability to measure only the predominant viral species and the fact that some mutations conferring significant resistance to one drug may actually increase viral susceptibility to a second, unrelated agent. The lack of a clear and reproducible relationship between in vitro and in vivo results, together with the high cost, represent further limitations to the widespread utilization of resistance testing.

9. Immune reconstitution and viral reservoirs

A remarkable amount of data have been recently produced, showing that a specific immune response is evoked by HIV during primary infection (Rosenberg et al., 1997). This consists in the appearance of p24 gag-specific T helper responses and cytotoxic T lymphocytes specific for viral antigens. The strength of CTL response appears to be a key factor in determining the viral setpoint, which in turn will predict the future outcome in the individual patient. This reactivity usually declines within the first months of infection, unless a potent antiretroviral treatment is initiated during the acute phase. Strong and persistent gag-specific T helper CD4 and CTL activity is maintained in a high proportion of subjects, whereas among patients having initiated HAART during the chronic phase the same proportion is around 5%, or even less in those with CD4+ cell count below 250/mmc. Unfortunately, early treatment, though able to keep plasma viral load to undetectable levels and to maintain a vigorous anti-HIV immune response, seems unable to prevent the establishment of a latent reservoir of HIV, represented by resting CD4+ T cells. These cells have a very long half-life (about 43 months, according to the most recent data (Finzi et al., 1999)), which accounts for the lifelong persistence

of HIV and the extremely long time (over 60 years) estimated to be required for viral eradication. For these reasons, new strategies are being designed. These include drugs like hydroxyurea or cyclosporine, which target the host cells, or new immunotherapeutic approaches, such as HIV vaccination or cytokine therapy, which might enhance virus specific immunity, allowing the control of any viruses released from the latent reservoir.

While incapable of restoring HIV specific immunity, HAART produces a dramatic increase in CD4+ cells which is associated with an improvement in immune reactivity to opportunistic agents, such as cytomegalovirus and tuberculosis. The mechanism for this immune restoration is a rapid recirculation of memory cells, followed by a slow generation of naïve CD4+ cells specific for ubiquitous and opportunistic pathogens. This occurs in the majority of subjects, across all stages of disease, and is the mechanism underlying the dramatic drop in the morbidity and mortality for opportunistic infections seen in all developed countries after the introduction of HAART (Autran et al., 1999).

10. New drugs in the pipeline

Currently, 15 antiretroviral agents are approved or available through expanded access programs, while there are at least 23 new drugs in clinical development that are expected to become available within the next three years. Several of them belong to the already well known classes (Reverse Transcriptase Inhibitors, Protease Inhibitors), and are characterized by higher potency and/or tolerability and/or better pharmacokinetic profile. Furthermore, in some cases they show antiviral activity also against HIV strains which are no longer sensitive to previous antiretroviral agents.

In the class of reverse transcriptase inhibitors the most promising nucleoside analogues are emitricitabine (FTC), PMPA, Iodenosine (F-ddA) and dOTC (BCH-10652), while emivirine GW420867X, AG 1549, calanolide A, and DMP 961-963 are the new non nucleoside reverse transcriptase inhibitors. The new Protease Inhibitors include several compounds, such as ABT 378, L-756,423 and tipranavir.

A second group of new antiretrovirals consists of drugs acting on different viral targets. The most advanced in development is T20, a fusion inhibitor which blocks de novo infection and cell-to-cell virus transmission and has entered phase 11 clinical development. The major disadvantage of T20 is related to its inactivation in the gastric environment; consequently it must be given i.v. or s.c. Other fusion inhibitors (AMD3100, FP-21399, PRO 542) are in earlier phases of development.

A further class of drugs includes the integrase inhibitors, which prevent the integration of viral DNA into the host DNA. Due to technical issues in the production of these molecules, their development has been slower than expected. Zintevir, the compound which is furthest along in development, is currently in phase I-II trials and is administered by intravenous infusion.

11. Conclusions

In spite of the huge advances in antiretroviral therapy, we are still far from having solved the problem of HIV infection. In fact, currently available regimens have limited potency and remarkable toxicity. Toxicity and complexity represent a challenge for patients' adherence. Furthermore, even though the number of theoretical drug combinations is large, cross reactivity among drugs of the same class makes the actual number of therapeutic options rather limited.

Better drugs, safer and easier to administer, with more favorable pharmacologic properties and activity against drug-resistant viruses are therefore needed. The validation of drug resistance testing for use in clinical practice will provide clinicians with a helpful tool for patients' management. Salvage therapies will hopefully be designed on the basis of individual resistance profiles, allowing for more specific treatments and, possibly, drug sparing.

The increasing evidence showing that future course and outcome of HIV infection mostly depend on events that take place during primary infection, make it necessary to concentrate all the efforts on the early diagnosis and treatment.

Though eradication does not appear a feasible goal, even with the most potent and early interventions, the evidence of a specific and effective cellular immune response against HIV points to the potential advantages of the immune manipulation. In this respect, drugs such as IL2 and the use of HIV-derived immunogens have provided some encouraging results (Chun et al., 1999; Davey et al., 1999; Valentine et al., 1999).

Finally, we cannot underestimate the fact that the impressive therapeutic gains in the management of HIV disease benefit only 10% of the HIV-infected global population. For the remaining 90%, it is very unlikely that prevention strategies or antiretroviral drugs will be available. Effective vaccination is the only approach that is likely to have a major effect on the AIDS epidemic in the developing world.

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